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(54) Title: CATALYST FOR ASYMMETRIC TRANSFER HYDROGENATION

(57) Abstract: The invention relates to a catalyst for asymmetrical transfer hydrogenation on the basis of a transition metal compound and a nitrogen-containing enantiomerically enriched ligand. The invention also relates to various processes for the preparation of enantiomerically enriched compounds using the catalyst according to the invention. In the catalyst according to the invention the transition metal is iridium, ruthenium, rhodium or cobalt and the enantiomerically enriched ligand contains sulphur in the form of a thioether or a sulphoxide, the sulphur being bound to the nitrogen via two or more carbon atoms. Surprisingly, it has been found that with the catalyst according to the invention a high conversion in a good enantiomeric excess of the enantiomerically enriched compound can be obtained. It has been found, in addition, that the catalyst with iridium as metal is also very stable in formic acid, so that formic acid can be used as the hydrogen donor, making the reaction irreversible and thereby allowing it to run to completion so that higher substrate concentrations can be used.

# CATALYST FOR ASYMMETRICAL TRANSFER HYDROGENATION

The invention relates to a catalyst for asymmetrical transfer hydrogenation on the basis of a transition metal compound and a nitrogen-containing enantiomerically enriched ligand. The invention also relates to various processes for the preparation of enantiomerically enriched compounds using the catalyst according to the invention.

Asymmetrical transfer hydrogenation is a method for the preparation of an enantiomerically enriched compound in which the presence of a transition metal catalyst containing an enantiomerically enriched ligand ensures that the double bond of a prochiral compound is asymmetrically reduced through hydrogen transfer with a hydrogen-donating organic compound. This is taken to mean at least that in the reaction product an excess of one of the enantiomers of the compound prepared is present. This excess will hereinafter be referred to as "enantiomeric excess" or e.e. (as determined by capillary GLC analysis over a chiral cycloSil-B column). The general advantage of such an asymmetrical transfer hydrogenation, for instance compared with reduction with molecular hydrogen, is that this reaction can take place under relatively mild conditions as regards temperature and pressure while the yield is relatively high and the by-product content low, so that the production costs can be low. In practice, this asymmetrical transfer hydrogenation is often employed for the preparation of enantiomerically enriched alcohols from prochiral ketones.

Such a catalyst is known from EP 0-916-637. In this known catalyst the nitrogen-containing

enantiomerically enriched ligand is a diamine, an amino alcohol or an aminophosphine compound and the transition metal is chosen from group VIII of the periodic system, this preferably being ruthenium.

The drawback of the known catalysts from EP 0-916-637, particularly the catalysts that contain amino-alcohol ligands, is that actually they are stable enough only when alcohols are used as the hydrogen donor. This poses an inherent problem in the reduction of ketones in that the enantiomeric purity is often too low due to the reversibility of the transfer hydrogenation reaction and, in addition, the chemical similarity of the hydrogen donor alcohol and the enantiomerically enriched alcohols formed. An acceptable enantiomeric excess is achieved only if a huge excess of the hydrogen-donating alcohol is added. This is disadvantageous since it results in relatively low space time yields being obtained using production equipment of a given size and since the huge excess must be separated and purified for reuse, which adversely affects process economics. A further disadvantage is that the known catalysts, particularly the catalysts that contain diamine and the aminophosphine ligands, often have a too low activity and are not enantioselective enough as a result of which the enantiomerically enriched compound obtained with it has a too low enantiomeric excess (e.e.).

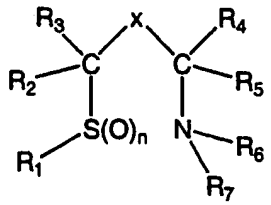
The aim of the invention therefore is to provide a catalyst for asymmetrical transfer hydrogenation that does not have the above-mentioned drawbacks.

This aim is achieved according to the invention in that the transition metal is iridium, ruthenium, rhodium or cobalt and the enantiomerically

enriched ligand contains sulphur in the form of a thioether or a sulphoxide, the sulphur being bound to the nitrogen via two or more carbon atoms.

Surprisingly, it has been found that very good results can be obtained with the catalyst according to the invention. Here and hereinafter this is taken to mean in particular a rapid and high conversion to a good enantiomeric excess (e.e.) of the enantiomerically enriched compound. Preferably, the transition metal in the catalyst is iridium. With this, very good results are obtained. The iridium catalyst according to the invention has been found to give rise to a very good enantiomeric excess and conversion besides being very stable. Surprisingly, it has also been found to be stable in formic acid, so that formic acid can also be used as the hydrogen donor. Since formic acid is converted to carbon dioxide gas in the reduction, transfer hydrogenation with this species is irreversible. In general, the use of a hydrogen donor that effects irreversible transfer hydrogenation (such as formic acid, partially unsaturated heterocycles and partially unsaturated hydrocarbons) is most advantageous since this allows the reaction to run to completion, thereby allowing the use of a much higher substrate concentration than when an alcohol is the hydrogen donor. Moreover, the irreversible nature of the reaction prevents racemization of the product. A further advantage of the specific case of formic acid/trialkylamine compared to alcohol as the hydrogen donor is that the reaction can take place in the air rather than under argon.

The enantiomerically enriched ligand in the catalyst according to the invention has a general molecular structure as indicated in the formula




where $R_1$ up to and including $R_7$ can each in principle be any substituent, it being understood that $R_1$ cannot be hydrogen, that n is 0 or 1 (thioether or sulphoxide), that one or both of $R_6$ and $R_7$ are hydrogen (secondary or primary amine) and that there must be at least one chiral centre in the molecule. Further, $R_1$ up to and including $R_7$ can for instance be a hydrogen (except for $R_1$), an alkyl, aryl, aralkyl, alkenyl or alkynyl group with 1-20 C-atoms, or a group containing one or more heteroatoms, e.g. O, N, P, or S, or functional groups. Each of the substituents $R_1$ up to and including $R_7$ can form a ring together with other substituents. The sulphur and/or the nitrogen themselves may also form part of a ring.

In general, the sulphur can be bound to the nitrogen via two or more carbon atoms. X can be nothing, so that the sulphur- containing group and the amine are vicinal, but may also contain one or more carbon or heteroatoms, in a ring or not. Examples are methionine-derived ligands with three carbon atoms between the nitrogen and the sulphur. If heteroatoms are present between the sulphur and the nitrogen group, these are preferably separated from the sulphur and the nitrogen by two or more carbon atoms. Preferably, in the catalyst according to the invention the sulphur is bound to the nitrogen via two carbon atoms. Such a catalyst has been found to have a higher activity.

The nitrogen in the enantiomerically enriched ligand is preferably an amine group. With a view to obtaining a good activity and enantioselectivity the amine group is substituted at most once (secondary amine), or, preferably, not substituted which means that $R_6$ or $R_7$ is hydrogen and that more preferably $R_6$ and $R_7$ are both hydrogen.

In the catalyst according to the invention the sulphur has the form of a thioether or a sulphoxide (n is 0 or 1). The sulphur is substituted with a group containing at least one carbon. Preferably, the sulphur is substituted with a substituted or non-substituted alkyl, (hetero)aryl or (hetero)aralkyl group. It is possible for a heteroatom to be present in the aromatic ring. Examples of suitable sulphur substituents are isopropyl, cyclohexyl, phenyl, benzyl, 2-phenethyl, naphthyl, thiophene and furan. This increases the reactivity and the e.e.

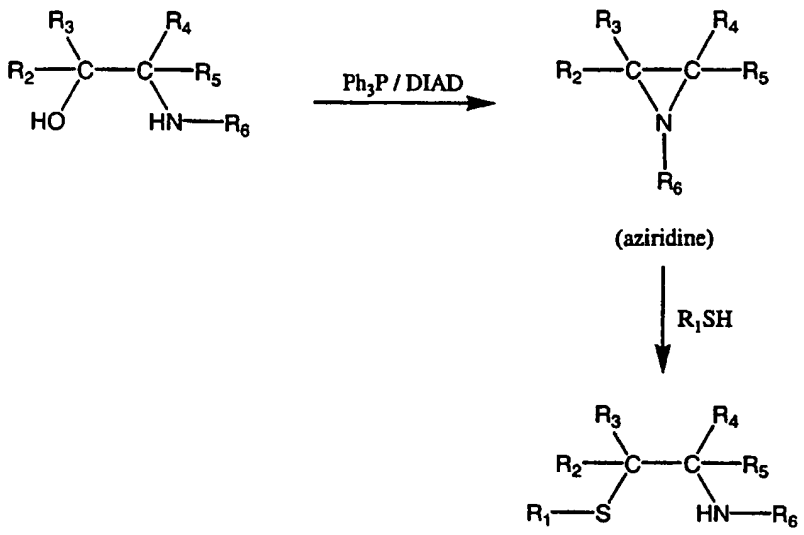
For a good enantioselective transfer hydrogenation the ligand in the catalyst according to the invention must be enantiomerically enriched. This is taken to mean that one of the enantiomers of the ligand is present in the catalyst in an excess. Preferably, the enantiomeric excess is more than 90%, more preferably more than 95% and most preferably more than 99%.

The chiral centre in the enantiomerically enriched active ligand in the catalyst according to the invention may in principle be present at various places, but preferably lies beside or near the nitrogen-containing group or the thioether group. In one embodiment the chiral centre is located at the carbon to which the nitrogen-containing group is bound. Such an enantiomerically enriched ligand can simply be derived from enantiomerically enriched cysteine (Table 1, ligand

1). This is an amino acid that is widely available and therefore inexpensive. Preferably, the carboxylic acid group is reduced to an alcohol group (Table 1, ligand 2). This embodiment has a higher activity. Preferably, however, of the two or more carbon atoms that bind the sulphur to the nitrogen at least the carbon bound to the sulphur is chiral. This has the advantage that a higher e.e. is obtained.

A particularly high e.e. is achieved if the enantiomerically enriched ligand in the catalyst according to the invention has two or more chiral centres. In a preferred embodiment of this catalyst the enantiomerically enriched ligand is a sulphoxide, with one of the two or more chiral centres being the sulphur of the sulphoxide (Table 1, ligand 3). This ligand is particularly attractive as it can be prepared in a simple manner by oxidation, for instance with peroxide, of an inexpensive starting material such as cysteine or the alcohol derived from it (Table 1, ligand 2), so that the ligand is very inexpensive. In another preferred embodiment of the catalyst in which the ligand has two or more chiral centres the enantiomerically enriched ligand is a thioether in which the carbon atoms to which the thioether and the amino group are bound are both chiral (for instance Table 1, ligands 4, 5 and 6). These catalysts have a high activity and give rise to a very high enantioselectivity.

The enantiomerically enriched ligands in the catalyst according to the invention can also very suitably be prepared by converting an enantiomerically enriched aziridine compound with a thiol compound. This reaction proceeds via a stereoselective ring opening so that an enantiomerically enriched thioether compound is obtained according to the following reaction scheme:




This method has the further advantage that the aziridine can be prepared in a simple manner by dehydration of an enantiomerically enriched vicinal amino alcohol, for instance with triphenylphosphine and DIAD (di-isopropyl azodicarboxylate). Enantiomerically enriched vicinal amino alcohols are often widely available and relatively inexpensive. Examples include ephedra-alkaloids, for instance ephedrine and norephedrine, and reduced amino acids. Preferably, therefore, in the catalyst according to the invention the enantiomerically enriched ligand is derived from an aziridine, itself derived from an enantiomerically enriched vicinal amino alcohol, by reaction with a thiol compound. An enantiomerically enriched ligand with a single chiral centre at the carbon beside the sulphur can for instance be prepared by conversion with a thiol compound of an aziridine derived from a reduced phenylglycine. In an embodiment that is more preferred the ligand has two chiral centres because the two carbons of the aziridine ring are substituted, the

ligand in the catalyst for instance being 2-amino-1-benzylthioether-1,2-diphenylethane. This ligand has a chiral centre at the carbon beside the sulphur and on the carbon beside the nitrogen. A catalyst with this ligand has a very good activity and gives rise to a very good enantioselectivity.

It has been found that in the case of a catalyst in which the ligand has two or more chiral centres (diastereomers) and in which the ligands form a diastereomeric mixture, asymmetrical transfer hydrogenation can take place if at least one of the diastereomers is enantiomerically enriched. Preferably, however, in that case too a single enantiomer of a single diastereomer is used to obtain the highest possible e.e.

The catalyst based on the transition metal compound and the enantiomerically enriched ligand can be applied in the form of separate components, one of which is the transition metal compound while another one is the enantiomerically enriched ligand, or as a complex containing the transition metal compound and the enantiomerically enriched ligand.

For the transition metal compound, use is preferably made of a catalyst precursor of the general formula

$$M_nX_pS_qL_r$$

where:

n is 1,2,3,4....;

p, q and r each independently represent 0,1,2,3,4...;

M is a transition metal ruthenium, iridium, rhodium or cobalt, most preferably iridium;

X is an anion such as, for instance, hydride, halide,

carboxylate, alkoxy, hydroxy or tetrafluoroborate; S is a so-called spectator ligand, a neutral ligand that is difficult to exchange, for instance an aromatic compound or an olefin, in particular a diene. Examples of aromatic compounds are: benzene, toluene, xylene, cumene, cymene, naphthalene, anisole, chlorobenzene, indene, dihydroindene, tetrahydronaphthalene, cholic acid, benzoic acid and phenylglycine. Examples of dienes are norbornadiene, 1,5-cyclooctadiene and 1,5-hexadiene. L is a neutral ligand, which can relatively easily be exchanged with other ligands, and is for instance a nitrile or a co-ordinating solvent, in particular acetonitrile, dimethylsulphoxide (DMSO), methanol, water, tetrahydrofuran, dimethylformamide, pyridine and N-methylpyrrolidinone.

Examples of suitable transition metal compounds are:
$[Ir(COD)Cl]_2$, $[Ir(CO)_2Cl]_n$, $[IrCl(CO)_3]_n$, $[Ir(Acac)(COD)]$, $[Ir(NBD)Cl]_2$, $[Ir(COD)(C_6H_6)]^+BF_4^-$, $[(CF_3C(O)CHC(O)CF_3)Ir(COE)_2]$, $[Ir(CH_3CN)_4]^+BF_4^-$, $[RuCl_2(\eta^6\text{-benzene})]_2$, $[RuCl_2(\eta^6\text{-cymene})]_2$, $[RuCl_2(\eta^6\text{-mesitylene})]_2$, $[RuCl_2(\eta^6\text{-hexamethylbenzene})]_2$, $[RuCl_2(\eta^6\text{-1,2,3,4-tetramethylbenzene})]_2$, $[RuBr_2(\eta^6\text{-benzene})]_2$, $[RuI_2(\eta^6\text{-benzene})]_2$, trans-$[RuCl_2(DMSO)_4]$, $[RuCl_2(PPh_3)_3]$, $[Rh(C_6H_{10})Cl]_2$ (in which $C_6H_{10}$ = hexa-1,5-diene), $[CoCl_2]$, $[Rh(COD)Cl]_2$.

Most preferably, the transition metal compound is $[Ir(COD)Cl]_2$. Very good results have been obtained with this.

The invention also relates to a process for the preparation of the catalyst according to the invention as described above, which involves the addition to a catalyst precursor, which contains the

transition metal, an anion and a spectator ligand that is difficult to exchange, of a nitrogen-containing enantiomerically enriched ligand containing sulphur in the form of a thioether or a sulphoxide, the sulphur being bound to the nitrogen via two or more carbon atoms. The catalyst can be prepared before it is used as an asymmetrical transfer hydrogenation catalyst or it can be formed in situ just before or during use, optionally in the presence of the reagents to be converted with the catalyst.

In a further embodiment, catalysts according to the invention can be made to be readily soluble in water or highly polar solvents. The catalysts of the invention can be rendered water-soluble by introducing water-soluble groups in the ligand, for instance, salts of carboxylic acids, salts of sulphonic acids and salts of phosphoric acids. Another possibility is the introduction of a trialkylammonium salt or a tetraalkylammonium salt in the ligand. A third group of substituents that can be introduced on the ligand are the neutral polar groups of which there may be various present in the molecule, such as alcohols and sulphoxides. Another way of rendering the catalyst water-soluble is to use bifunctional counter ions for the metal, for instance biscarboxylic acids, bisphosphates and bissulphonates. One of the two acid groups then serves as counter ion for the metal, while the other acid group is present as the salt of for instance sodium, potassium or lithium and imparts water solubility. It is also possible to introduce water-soluble groups on the spectator ligand. The advantage of a water-soluble catalyst is that the transfer hydrogenation reaction can be carried out in a two-phase system, for instance a (more) polar aqueous phase and a

(less polar) organic phase such as water/organic solvent, with the catalyst and the reducing agent being in the aqueous phase and the starting material and the product in the organic phase. As a result, the catalyst can very simply be separated from the product. A mixture of triethylamine and formic acid can also be chosen as the more polar phase. An example is the reduction of ketones in a two-phase system, with the more polar phase comprising an azeotropic mixture of triethylamine and formic acid, and the less polar phase comprising the ketone and the alcohol formed therefrom, optionally in the presence of a non-water-miscible solvent. At the end of the reaction the product can simply be separated by phase separation and the more polar phase can, after addition of extra formic acid, be reused in the reduction of a new batch of ketone. Another example of a more polar phase is ionic liquids. Examples of these are salts of imidazole such as 1-hexyl-3-methyl-imidazolium salts or N-alkyl pyridinium salts. These compounds are characterized by the fact that they are liquids at room temperature.

The invention also relates to a process for the preparation of an enantiomerically enriched compound from the corresponding prochiral compound via catalytic asymmetrical transfer hydrogenation in the presence of a hydrogen donor and the catalyst according to the invention as described above. The process can for instance very suitably be used in the preparation of enantiomerically enriched alcohols, hydrazines or amines starting from the corresponding prochiral ketones and, respectively, hydrazones, oxime derivatives or imines.

The catalysts of the invention can also advantageously be used for the kinetic resolution of carbonyl compounds - e.g. ketones or aldehydes - or

imines, oximes or hydrazones which already contain at least one chiral centre elsewhere in the molecule and are present in racemic form. Reduction of the carbonyl compounds, imines, oximes or hydrazones then most preferably takes place only in one of the two enantiomeric forms. By terminating the reaction when approximately 50% conversion is achieved, the ketone (aldehyde, imine, oxime, hydrazone) can be recovered substantially in the one enantiomeric form; the other enantiomer has then substantially been converted to the corresponding alcohol, amine or hydrazine.

The catalysts of the invention can also be advantageously used for the kinetic resolution of a racemic alcohol by oxidation in the presence of the catalyst according to the invention. In this reaction it is higly preferred for only one of the enantiomers of the alcohol to be oxidised, so that after about 50% conversion a mixture has formed of the alcohol, consisting substantially of a single enantiomer, and the corresponding ketone, which has been formed from the other enantiomer. Suitable oxidants for this are ketones or aldehydes, for instance acetone or chloral(hydrate).

The catalysts of the invention can also be advantageously used for the desymmetrization of *meso* diols by oxidation in the presence of the catalyst according to the invention. In this reaction the *meso* diol is oxidised to a hydroxy ketone in a stereoselective manner such that the product hydroxy ketone consists substantially of a single enantiomer.

The catalysts of the invention can also in principle be advantageously used for the preparation of a ketone in an enantiomeric excess from a racemic alcohol which contains a further chiral racemic centre that is not bound to the OH group by oxidation in the

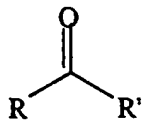
presence of the catalyst according to the invention so that after about 50% conversion a mixture has formed of the enantiomerically enriched ketone (formed substantially from one of the two absolute configurations at the chiral centre not bound to the OH group) and two enantiomerically enriched diastereomers of the alcohol, consisting substantially of the other absolute configuration at the chiral centre not bound to the OH group.

However, if the chiral centre that is not bound to the OH group is enantiomerically enriched, then oxidation by the catalyst according to the invention yields a ketone which is enantiomerically enriched. However, the catalyst according to the invention can in principle be used to selectively oxidise one of the two diastereomers which are epimeric at the carbon bound to the OH group, so that after about 50% conversion a mixture has formed of the enantiomerically enriched ketone (formed substantially from one of the two enantiomerically enriched epimers) and the diastereomerically enriched alcohol (consisting substantially of the other enantiomerically enriched epimer).

The invention also relates to a process for the preparation of an enantiomerically enriched compound with two or more chiral, non racemic centres in which a chiral, non racemic ketone, imine, oxime or hydrazone is reduced in the presence of a catalyst according to the invention. In this process the ketone (imine, oxime, hydrazone) is fully reduced to a compound with substantially only one relative configuration between the existing chiral, non racemic centre(s) and the new chiral, non racemic centre.

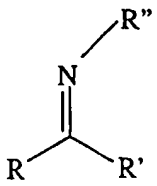
As prochiral compounds use can for instance

be made of prochiral ketones of the general formula:



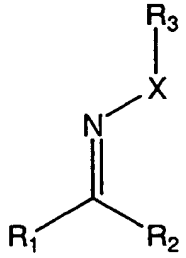
where R and R' are not the same and each independently represent an alkyl, aryl, aralkyl, alkenyl or alkynyl group with 1-20 C-atoms or together they form a ring along with the carbonyl C-atom to which they are bound, it being possible for R and R' to also contain one or more heteroatoms or functional groups. Suitable examples of prochiral ketones include acetophenone, 1-acetonaphthone, 2-acetonaphthone, 3-quinuclidinone, 2-methoxycyclohexanone, 1-phenyl-2-butanone, benzyl-isopropyl ketone, benzyl acetone, cyclohexyl-methyl ketone, *tert*-butyl-methyl ketone, *tert*-butyl-phenyl ketone, isopropyl-phenyl ketone, ethyl-(n-propyl) ketone, o, m or p-methoxy acetophenone, o, m or p-(fluoro-, chloro-, bromo- or iodo-) acetophenone, o, m or p-cyano-acetophenone, o, m or p-nitro-acetophenone, 2-acetylfluorene, acetylferrocene, 2-acetylthiophene, 3-acetylthiophene, 2-acetylpyrrole, 3-acetylpyrrole, 2-acetylfuran, 3-acetylfuran, 1-indanone, 2-hydroxy-1-indanone, 1-tetralone, p-methoxyphenyl-p'-cyanophenylbenzophenone, cyclopropyl-(4-methoxyphenyl) ketone, 2-acetylpyridine, 3-acetylpyridine, 4-acetylpyridine, acetylpyrazine;

prochiral imines of the general formula:



where R, R' and R" for instance each independently represent an alkyl, aryl, aralkyl, alkenyl or alkynyl group with 1-20 C-atoms or form a ring together with the atoms to which they are bound, it being possible for R , R' and R" to also contain one or more heteroatoms and functional groups, and R" may in addition be a group to be split off. Suitable prochiral imines may be prepared from the above-described ketones and an alkyl amine, aralkyl amine or aryl amine or an amino acid derivative, for instance an amino acid amide, an amino acid ester, a peptide or a polypeptide. Examples of suitable alkyl amines, aralkyl amines and aryl amines are a benzyl amine, for instance benzyl amine, or an o-, m- or p-substituted benzyl amine, an α-alkyl benzyl amine, a naphthyl amine, for instance naphthyl amine, a 1-,2-,3-,4-,6-,7-,8- or 9-substituted naphthyl amine and a 1-(1-naphthyl)alkyl amine or a 1-(2-naphthyl)alkyl amine. Suitable imines are for instance N-(2-ethyl-6-methylphenyl)-1-methoxy-acetonimine, 5,6-difluoro-2-methyl-1,4-benzoxazine, 2-cyano-1-pyrroline, 2-ethyoxycarbonyl-1-pyrroline, 2-phenyl-1-pyrroline, 2-phenyl-3,4,5,6-tetrahydropyridine and 3,4-dihydro-6,7-dimethoxy-1-methyl-isoquinoline;

oximes or hydrazones of the general formula




where

- X contains a heteroatom and represents NH, NR or

O, for instance, with R representing an alkyl, aryl, aralkyl, alkenyl or alkynyl group with 1-20 C-atoms.

- $R_1$ and $R_2$ each independently represent an alkyl, aryl, aralkyl, alkenyl or alkynyl group with 1-20 C-atoms, or form a ring with each other or with $R_3$ and the atoms to which they are bound, which groups may also contain one or more heteroatoms and/or functional groups.
- in the case of an oxime or oxime ether, $R_3$ is H or an alkyl, aryl, aralkyl, alkenyl or alkynyl group with 1-20 C-atoms, which groups may also contain one or more heteroatoms and/or functional groups; and in the case of a hydrazone it is H, an alkyl, aryl, alkenyl, alkynyl, acyl, phosphonyl or sulphonyl group with 0-20 C-atoms, which groups may also contain one or more heteroatoms and/or functional groups.

The process according to the invention is carried out in the presence of one or more hydrogen donors, which in the framework of this invention are understood to mean compounds that can in any way transfer hydrogen to the substrate, for instance thermally or catalytically. Examples of suitable hydrogen donors that can be used are aliphatic or aromatic alcohols, in particular secondary alcohols with 1-10 C-atoms, for instance 2-propanol and cyclohexanol, acids, for instance formic acid, $H_3PO_2$, $H_3PO_3$ and salts thereof, partially unsaturated hydrocarbons, partially unsaturated heterocyclic compounds, hydroquinone or reducing sugars. Preferably, 2-propanol or formic acid is used. The molar ratio of substrate to hydrogen donor preferably lies between 1:1 and 1:100.

In the asymmetrical transfer hydrogenation

use is preferably made of a molar ratio of metal present in the transition metal compound to substrate of between 1:10 and 1:1,000,000, in particular between 1:100 en 1:100,000.

The temperature at which the asymmetrical transfer hydrogenation is carried out in general is a compromise between the reaction velocity on the one hand and the degree of racemisation on the other, and preferably lies between -20 and 100°C, in particular between 0 and 60°C. The asymmetrical transfer hydrogenation can in principle be carried out in an oxygen-containing atmosphere; preferably, however, the asymmetrical transfer hydrogenation is carried out in an inert atmosphere, for instance under nitrogen.

As solvent in principle any solvent can be used that is inert in the reaction mixture. In a preferred embodiment a solvent is used that also serves as hydrogen donor, for instance 2-propanol. If the asymmetrical transfer hydrogenation is carried out in water, with a 2-phase system being formed, preferably a water-soluble catalyst is used. The catalyst for the asymmetrical transfer hydrogenation can if desired be activated by hydrogenation with hydrogen or by treatment with a base, for instance an alkali (alkaline earth) compound, for instance an alkali (alkaline earth) hydroxide, an alkali (alkaline earth) carboxylate or an alkali (alkaline earth) alkoxide with 1-20 C-atoms, as alkali metal for instance Li, Na or K being used and as alkaline earth metal for instance Mg or Ca. Suitable bases are for instance sodium hydroxide, potassium hydroxide, potassium-t-butoxide and magnesium methoxide.

In the preparation of the catalyst the molar ratio of metal to the enantiomerically enriched ligand

is preferably chosen to be between 2:1 and 1:10, preferably between 1:1 and 1:6.

As the hydrogen donor in the process according to the invention, use is advantageously made of a hydrogen donor that effects irreversible transfer hydrogenation. An example of such a hydrogen donor is formic acid or a formic acid salt, preferably in combination with triethylamine. In this case the formic acid decomposes and carbon dioxide gas is formed in the transfer hydrogenation reaction and, this being outside the reaction equilibrium, the reaction runs to completion. With these hydrogen donors that effect irreversible transfer hydrogenation, a higher substrate concentration can be chosen compared to an alcohol such as isopropanol.

Preferably, the concentration of prochiral compound is at least 0.2, more preferably at least 0.5 and even more preferably at least 0.7 mol per litre of the hydrogen donor. Under these conditions the catalyst according to the invention has been found to be stable, in particular when iridium is used as the transition metal.

The invention will be elucidated with reference to the examples, without however being restricted thereto.

Examples I up to and including XIX and comparative experiments C1 up to and including C3

Various catalysts according to the invention were prepared and tested for their enantioselectivity and conversion under different conditions, the ligands, the hydrogen donor, the catalyst precursor and the prochiral compound being varied. In comparative experiments C1 up to and including C3, with a catalyst

according to the invention with a very good performance, the sulphur in the enantiomerically enriched ligand (ligand 6) was replaced with oxygen (ligand 7). In all experiments use was invariably made of the standard set of conditions as defined below. The variations in these standard conditions used are given with the results below Table 2.

The reaction with formic acid as hydrogen donor proceeds as follows: a solution of $[IrCl(COD)]_2$ (0.01 mmol, 6.7 mg) as catalyst precursor (COD is cyclooctadiene), 0.05 mmol ligand and 4 mmol acetophenone as substrate was heated at 65°C for 30 min under argon. The argon supply was stopped and 3 ml of a 5/2 azeotropic mixture of formic acid (as hydrogen donor) and triethylamine was added in air. The reaction proceeded at 60 °C in an open vessel for the indicated time.

The reaction with 2-propanol as hydrogen donor proceeds as follows: the solution of $[IrCl(COD)]_2$ (0.01 mmol, 6.7 mg), 0.05 mmol of the ligand and 5 ml 2-propanol were heated at 80°C for 30 min. After cooling to room temperature the mixture was diluted with 33.75 ml 2-propanol and 4 mmol acetophenone and t-BuOK (1.25 ml, 0.1M in propan-2-ol, 0.125 mmol). The reaction was carried out at room temperature under argon for the indicated time.

The enantiomeric excess of the 1-phenethyl alcohol formed was determined by means of capillary GLC using a Carlo Erba GC 6000 Vega 2 with a 25 m Cyclosil-B (chiral) column. The enantiomeric excess is defined as (([R] - [S]) / ([R] + [S]))*100%, where [R] and [S] are the concentrations of the R enantiomer and the S enantiomer. The conversion, expressed as the percentage of acetophenone converted in one hour, was determined by

means of GLC. The optical rotation was determined using a Perkin-Elmer 241 automatic polarimeter.

The ligands used are presented in Table 1 (Bn is benzyl, iPr is isopropyl, Ph is phenyl) and described below. The results of the examples according to the invention and the comparative experiments are shown in Table 2.

S-Benzyl-(*R*)-cysteinol sulfoxide (3)

Hydrogen peroxide (30% in water, 5 mmol, 0.51 ml) was added to S-benzyl-(*R*)-cysteinol in methanol (1 g, 5 mmol), at -70 °C. The reaction mixture was slowly warmed to room temperature and stirred overnight. It was evaporated to dryness to yield a white solid (100%). The two diastereomers were separated by repeated crystallisation from ethanol.

S-Benzyl-(*R*)-cysteinol (*S*)-sulfoxide (3(*S,R*))

M.p.: 130-133 °C. IR (KBr): ν ($cm^{-1}$) = 3329, 3270, 3108, 2925, 1600, 1495, 1454, 1096, 1071, 1029, 985, 700. $^1H$ NMR ($CD_3OD$): δ = 2.73 (1H, dd, *J* = 7.0 Hz, 13.2 Hz, S(O)C$H_2$), 2.96 (1H, dd, *J* = 6.0 Hz, 13.2 Hz, S(O)C$H_2$), 3.31 (1H, m, C*H*), 3.54 (1H, d, *J* = 5.4 Hz, C$H_2$-OH), 3.55 (1H, d, *J* = 5.4 Hz, C$H_2$-OH), 4.05 (1H, d, *J* = 13.0, Ph-C$H_2$), 4.22 (1H, d, *J* = 13.0, Ph-C$H_2$), 7.37 (5H, s, $C_6H_5$). $^{13}C$ NMR ($CDCl_3$): δ = 49.48 (*C*H), 54.38, 58.60, 65.25 (3 *C*$H_2$), 128.62, 129.00, 130.20 (*C*$H_{arom}$), 129.31 ($C_q$). HRMS ($FAB^+$): *m/z* calcd for $C_{10}H_{16}NO_2S$ $[M+H]^+$: 214.0902. Found: 214.0910. Anal. Calcd for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09; N, 6.57; S, 15.03. Found: C, 55.97; H, 7.01; N, 6.48; S, 14.62.

$[\alpha]^{20}_D$ = -46° (*c* = 0.51, EtOH).

S-Benzyl-(*R*)-cysteinol (*R*)-sulfoxide (3(*R*,*R*))

M.p.: 128-129 °C. IR (KBr): ν ($cm^{-1}$) = 3311, 3274, 3186, 2886, 1611, 1494, 1453, 1364, 1069, 1025, 1002, 992, 762, 689. $^1H$ NMR ($CD_3OD$): δ = 2.74 (1H, dd, *J* = 9.6 Hz, 13.2 Hz, S(O)C*H*$_2$), 2.85 (1H, dd, *J* = 3.6 Hz, 13.2 Hz, S(O)C*H*$_2$), 3.28 (1H, m, C*H*), 3.52 (1H, dd, *J* = 5.7 Hz, *J* = 10.9 Hz, C*H*$_2$-OH), 3.55 (1H, dd, *J* = 5.4 Hz, *J* = 13.9 Hz, C*H*$_2$-OH), 4.07 (1H, d, *J* = 12.9, Ph-C*H*$_2$), 4.19 (1H, d, *J* = 13.0, Ph-C*H*$_2$), 7.37 (5H, s, C$_6$*H*$_5$). $^{13}C$ NMR ($CDCl_3$): δ = 48.03 (*C*H), 55.26, 58.35, 66.07 (3 *C*H$_2$), 128.60, 129.03, 130.20 (*C*H$_{arom}$), 129.51 (*C*$_q$). HRMS ($FAB^+$): *m/z* calcd for $C_{10}H_{16}NO_2S$ $[M+H]^+$: 214.0902. Found: 214.0904. Anal. Calcd for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09; N, 6.57; S, 15.03. Found: C, 55.85; H, 7.07; N, 6.37, S, 14.98. $[\alpha]^{20}_D$ = +16° (*c* = 0.9, EtOH).

(1*R*, 2*S*)-2-Amino-1-phenyl-1-isopropylthio-propane (4)

A slight excess of isopropylmercaptan was added to a solution of (2*S*, 3*S*)-3-methyl-2-phenylaziridine in methanol. The solution was stirred overnight at 65 °C. The solvent and the excess isopropylmercaptan were removed under reduced pressure. The product was obtained as a light yellow oil after column chromatography (silica gel 60, eluent: dichloromethane / 5% methanol, $R_f$-value: 0.40). Yield: 32%. IR (neat): ν ($cm^{-1}$) = 3363, 3060, 3026, 2962, 2925, 1452, 734, 701. $^1H$ NMR ($CDCl_3$): δ = 1.12 (3H, d,

*J* = 6.8 Hz, $CH_3$), 1.17 (3H, d, *J* = 6.4 Hz, $CH_3$), 1.22 (3H, d, *J* = 6.5 Hz, $CH_3$), 1.32 (2H, bs, $NH_2$), 2.54, (1H, m, $CH(CH_3)_2$), 3.24 (1H, m, $(CH_3)CH$), 3.74 (1H, d, *J* = 6.6 Hz, (Ph)*CH*), 7.17-7.50 (m, 5 H, $C_6H_5$). $^{13}C$ NMR ($CDCl_3$): δ = 21.67, 23.28, 23.80 (3 $CH_3$), 34.49, 51.69, 57.63 (3 *CH*), 127.33, 128.52, 128.93 ($CH_{arom}$), 140.68 ($C_q$). HRMS ($FAB^+$): *m/z* calcd for $C_{12}H_{20}NS$ $[M+H]^+$: 210.1316. Found: 210.1315. $[\alpha]^{20}_D$ = -151° (*c* = 0.84, $CHCl_3$).

(1*R*, 2*S*)-2-Amino-1-phenyl-1-benzylthio-propane (5)

A slight excess of benzylmercaptan was added to a solution of (2*S*, 3*S*)-3-methyl-2-phenylaziridine in methanol. The solution was stirred overnight at 65 °C. The solvent was removed under reduced pressure. The product was obtained as a light yellow oil after column chromatography (silica gel 60, eluent: dichloromethane / methanol: 9/1, $R_f$-value: 0.38). Yield: 73%. IR (neat): ν ($cm^{-1}$) = 3367, 3060, 3028, 2964, 2924, 1600, 1492, 1452, 910, 735, 701. $^1H$ NMR ($CDCl_3$): δ = 1.12 (3H, d, *J* = 6.4 Hz, $CH_3$), 1.27 (2H, bs, $NH_2$), 3.22, (1H, m, *CH*), 3.36 (1H, d, *J* = 13.3 Hz, $CH_2$), 3.52 (1H, d, *J* = 6.9 Hz, *CH*), 3.53 (1H, d, *J* = 13.3 Hz, $CH_2$), 7.15-7.35 (m, 10 H, $C_6H_5$). $^{13}C$ NMR ($CDCl_3$): δ = 21.69 ($CH_3$), 35.63 ($CH_2$), 51.33, 58.06 (2 *CH*), 127.10, 127.53, 128.54, 128.61, 129.13, 129.25 ($CH_{arom}$), 138.36, 140.00 (2 $C_q$). HRMS ($FAB^+$): *m/z* calcd for $C_{16}H_{20}NS$ $[M+H]^+$: 258.1316. Found: 258.1317. $[\alpha]^{20}_D$ = -32° (*c* = 0.99, $CHCl_3$).

(1*R*, 2*S*)-2-Amino-1,2-diphenyl-1-benzylthio-ethane (6)

A slight excess of benzylmercaptan was added to a solution of (2*S*, 3*S*)-2,3-diphenylaziridine in methanol. The reaction mixture was stirred for 3 days in refluxing methanol. The solvent was removed under reduced pressure. The product was obtained as a light yellow oil after column chromatography (silica gel 60, eluent: ethyl acetate / hexane: 1/1, $R_f$-value: 0.37). Yield: 38%. IR (neat): ν ($cm^{-1}$) = 3370, 3061, 3028, 2918, 1601, 1493, 1463, 735, 700. $^1H$ NMR ($CDCl_3$): δ = 1.55 (2H, bs, $NH_2$), 3.28, (2H, d, *J* = 5.6 Hz, $CH_2$), 3.82 (1H, d, *J* = 8.1 Hz, *CH*), 4.26 (1H, d, *J* = 8.1 Hz, *CH*), 7.08-7.30 (m, 15 H, $C_6H_5$). $^{13}C$ NMR ($CDCl_3$): δ = 36.05 ($CH_2$), 56.97, 60.96 (2 *CH*), 127.12, 127.67, 127.75, 127.88, 128.43, 128.53, 128.72, 129.21 ($CH_{arom}$), 138.02, 139.82, 142.92 (3 $C_q$). HRMS ($EI^+$): *m/z* calcd for $C_{21}H_{21}NS$ $[M]^+$: 319.1395. Found: 319.1399. $[\alpha]^{20}_D$ = +110° (*c* = 0.62, $CHCl_3$).

(1*R*, 2*S*)-2-Amino-1-phenyl-1-(2'-phenylethylthio)-propane (8)

A slight excess of 2-phenylethylmercaptan was added to a solution of (2*S*, 3*S*)-3-methyl-2-phenylaziridine in methanol. The solution was stirred for three days at 65 °C. The solvent was removed under reduced pressure. The product was obtained as a colourless oil after column chromatography (silica gel 60, eluent: diethyl ether, $R_f$-value: 0.19). Yield: 35%. $^1H$ NMR ($CDCl_3$): δ = 1.19 (3H, d, *J* = 6.4 Hz, $CH_3$), 1.44 (2H, bs, $NH_2$), 2.50, (2H, t, *J* = 7.3 Hz, $CH_2$), 2.68-

2.82 (2H, m, $CH_2$), 3.18-3.31 (1H, m, $(CH_3)CH$), 3.66 (1H, d, $J$ = 7.4 Hz, $(Ph)CH$), 7.01-7.10 (2H, m, $CH_{arom}$), 7.16-7.31 (4H, m, $CH_{arom}$), 7.31-7.39 (4H, m, $CH_{arom}$). $^{13}C$ NMR ($CDCl_3$): $\delta$ = 21.59 (q, $CH_3$), 32.68 (t, $CH_2$), 36.13 (t, $CH_2$), 51.26 (d, $CH$), 58.70 (d, $CH$), 126.21 (d, $CH_{arom}$), 127.35 (d, $CH_{arom}$), 128.32 (d, $CH_{arom}$), 128.42 (d, $CH_{arom}$), 128.84 (d, $CH_{arom}$), 139.90 (s, $C_q$), 140.44 (s, $C_q$).

(1*R*, 2*S*)-2-Amino-1-phenyl-1-cyclohexylthio-propane (9)

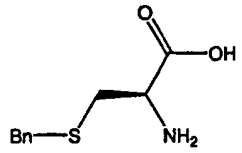
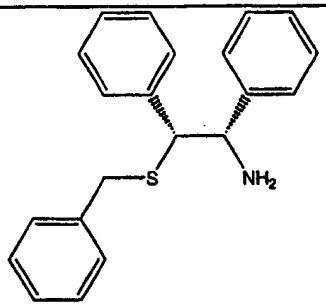
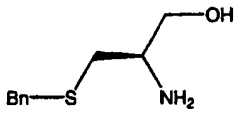
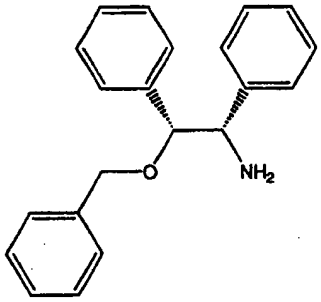
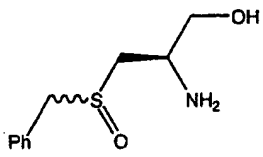
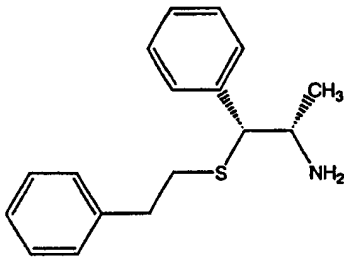
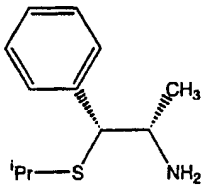
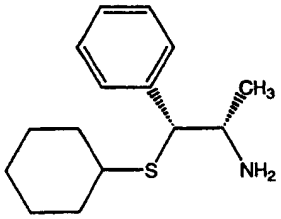
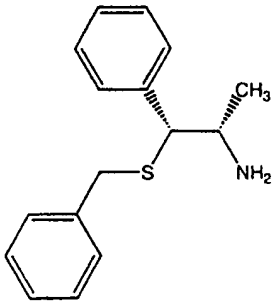
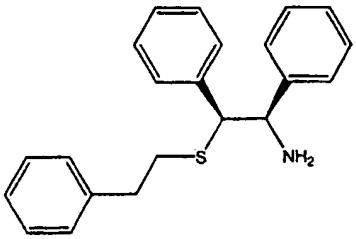
A slight excess of cyclohexylmercaptan was added to a solution of (2*S*, 3*S*)-3-methyl-2-phenylaziridine in methanol. The solution was refluxed overnight. The solvent was removed under reduced pressure. The product was obtained as a colourless oil after column chromatography (silica gel 60, eluent: diethyl ether, $R_f$-value: 0.14). Yield: 41%. $^1H$ NMR ($CDCl_3$): $\delta$ = 1.15 (3H, d, $J$ = 6.4 Hz, $CH_3$), 1.04-1.37 (6H, m, $C_6H_{11}$), 1.53 (2H, bs, $NH_2$), 1.60-1.81 (3H, m, $C_6H_{11}$), 1.86-2.02 (1H, m, $C_6H_{11}$), 2.24-2.43 (1H, m, $C_6H_{11}$), 3.17-3.30 (1H, m, $(CH_3)CH$), 3.77 (1H, d, $J$ = 6.5 Hz, $(Ph)CH$), 7.19-7.41 (5H, m, $CH_{arom}$). $^{13}C$ NMR ($CDCl_3$): $\delta$ = 21.40 (q, $CH_3$), 25.75 (t, $CH_2$), 25.96 (t, $CH_2$), 33.38 (t, $CH_2$), 33.81 (t, $CH_2$), 42.91 (d, CH), 51.52 (d, CH), 56.87 (d, $CH$), 127.08 (d, $CH_{arom}$), 128.29 (d, $CH_{arom}$), 128.69 (d, $CH_{arom}$), 140.69 (s, $C_q$).

(1*S*, 2*R*)-2-Amino-1,2-diphenyl-1-(2'-phenylethylthio)-ethane (10)

A slight excess of 2-phenylethylmercaptan

was added to a solution of (2*R*, 3*R*)-2,3-diphenylaziridine in methanol. The solution was refluxed for six days. The solvent was removed under reduced pressure. The product was obtained as a light yellow oil after column chromatography (silica gel 60, eluent: ethyl acetate / hexane: 1/1). Yield: 48%. $^{1}H$ NMR ($CDCl_3$): $\delta$ = 1.86 (2H, bs, $NH_2$), 2.33, (2H, t, $J$ = 7.4 Hz, $CH_2$), 2.57-2.64 (2H, m, $CH_2$), 3.99 (1H, d, $J$ = 8.5 Hz, $CH$), 4.26 (1H, d, $J$ = 8.3 Hz, $CH$), 6.88-7.00 (4H, m, $CH_{arom}$), 7.11-7.25 (7H, m, $CH_{arom}$), 7.24-7.37 (4H, m, $CH_{arom}$). $^{13}C$ NMR ($CDCl_3$): $\delta$ = 32.84 (t, $CH_2$), 35.93 (t, $CH_2$), 57.62 (d, $CH$), 60.85 (d, $CH$), 126.12 (d, $CH_{arom}$), 127.34 (d, $CH_{arom}$), 127.52 (d, $CH_{arom}$), 127.67 (d, $CH_{arom}$), 128.24 (d, $CH_{arom}$), 128.38 (d, $CH_{arom}$), 128.47 (d, $CH_{arom}$), 128.86 (d, $CH_{arom}$), 139.57 (s, $C_q$), 140.40 (s, $C_q$), 142.64 (s, $C_q$).

Table 1

| No. | ligand | No. | ligand |
|---|---|---|---|
| 1 |  | 6 |  |
| 2 |  | 7 |  |
| 3 |  | 8 |  |
| 4 |  | 9 |  |
| 5 |  | 10 |  |

| Example | Ligand | time (h) | conv. (%) | e.e. (%) | conf. (S/R) |
|---|---|---|---|---|---|
| I[1)] | 1 | 1 | 26 | 12 | S |
| II[1)] | 2 | 1 | 98 | 12 | S |
| III[1)] | 3(1:1) | 1 | 56 | 35 | S |
| IV[1)] | 3(S,R) | 1 | 56 | 27 | R |
| V[1)] | 3(R,R) | 0,5 | 99 | 65 | S |
| VI[1)] | 4 | 3 | >99 | 41 | S |
| VII[1)] | 5 | 3 | >99 | 65 | S |
| VIII[2)] | 5 | 1 | 96 | 65 | S |
| IX[2)] | 4 | 1 | 88 | 73 | S |
| X[2)] | 6 | 1 | 82 | 80 | R |
| XI[1)3)] | 3(R,R) | 1 | >99 | 79 | S |
| XII[1)3)] | 5 | 1 | >99 | 79 | S |
| XIII[2)3)] | 6 | 1 | >99 | 97 | R |
| XIV[2)4)] | 6 | 1 | 95 | 92 | R |
| XV[2)5)] | 5 | 2 | 44 | 49 | |
| XVI[2)6)] | 5 | 20 | 38 | 57 | |
| XVII[2)] | 8 | 1 | 96 | 77 | S |
| XVIII[2)] | 9 | 1 | 95 | 80 | S |
| XIX[2)] | 10 | 1 | 91 | 83 | R |
| C1 | 7 | 20 | <1 | - | |
| C2[2)] | 7 | 20 | 22 | - | |
| C3[2)5)] | 7 | 20 | 54 | 27 | |

1) formic acid / triethylamine used as hydrogen donor
2) 2-propanol used as hydrogen donor
3) substrate is 1-naphthyl-methyl ketone
4) substrate is phenyl-ethyl ketone
5) catalyst precursor is $[Ru(p\text{-}Cy)Cl_2]_2$
6) catalyst precursor is $[Rh(COD)Cl]_2$

CLAIMS

1. Catalyst for asymmetrical transfer hydrogenation on the basis of a transition metal compound and a nitrogen-containing enantiomerically enriched ligand, characterized in that the transition metal is iridium, ruthenium, rhodium or cobalt and the enantiomerically enriched ligand contains sulphur in the form of a thioether or a sulphoxide, the sulphur being bound to the nitrogen via two or more carbon atoms.

2. Catalyst according to claim 1, characterized in that the transition metal is iridium.

3. Catalyst according to claim 1 or claim 2, characterized in that the sulphur is bound to the nitrogen via two carbon atoms.

4. Catalyst according to any one of claims 1 - 3, characterized in that of the two or more carbon atoms that bind the sulphur to the nitrogen at least the carbon bound to the sulphur is chiral.

5. Catalyst according to any one of claims 1 - 4, characterized in that the enantiomerically enriched ligand has two or more chiral centres.

6. Catalyst according to claim 5, characterized in that the enantiomerically enriched ligand is a sulphoxide, one of the two or more chiral centres being the sulphur of the sulphoxide.

7. Catalyst according to claim 5, characterized in that the enantiomerically enriched ligand is a thioether in which the carbon atoms to which the thioether and the amino group are bound are both chiral.

8. Catalyst according to any one of claims 5 - 7, characterized in that the enantiomerically enriched ligand is a single diastereomer form.

9. Catalyst according to any one of claims 1 - 8, characterized in that the sulphur is substituted with a substituted or non-substituted (hetero)aryl, (hetero)aralkyl, or alkyl group.

10. Catalyst according to any one of claims 1 - 9, characterized in that the enantiomerically enriched ligand is derived from enantiomerically enriched cysteine.

11. Catalyst according to any one of claims 1 - 9, characterized in that the enantiomerically enriched ligand is derived by reaction of an enantiomerically enriched aziridine converted with a thiol compound.

12. Process for the preparation of a catalyst according to any one of claims 1-11, characterized in that it involves the addition to a catalyst precursor, which contains the transition metal, an anion and a spectator ligand that is difficult to exchange, of a nitrogen-containing enantiomerically enriched ligand which contains sulphur in the form of a thioether or a sulphoxide, the sulphur being bound to the nitrogen via two or more carbon atoms.

13. Process for the preparation of an enantiomerically enriched compound from the corresponding prochiral compound via catalytic asymmetrical transfer hydrogenation in the presence of a catalyst and a hydrogen donor, characterized in that use is made of a catalyst according to any one of claims 1-11.

14. Process according to claim 13, in which a prochiral ketone, imine, oxime or hydrazone is used as the prochiral compound.

15. Process for the kinetic resolution of a chiral, racemic ketone, aldehyde, imine, oxime or hydrazone, in which one enantiomer of the chiral, racemic ketone, aldehyde, imine, oxime or hydrazone is stereoselectively reduced in the presence of a catalyst according to any one of claims 1-11.

16. Process for the preparation of an enantiomerically enriched compound with two or more chiral centres in which a chiral, non racemic ketone, imine, oxime or hydrazone is diastereomerically reduced in the presence of a catalyst according to any one of claims 1-11.

17. Process for the kinetic resolution of a racemic alcohol by preferential oxidation of one of the enantiomers of the alcohol in the presence of the catalyst according to any one of claims 1-11.

18. Process for the preparation of a hydroxy ketone in an enantiomeric excess by oxidation of a *meso* diol in the presence of the catalyst according to any one of claims 1-11.

19. Process for the preparation of a ketone and/or an alcohol in an enantiomeric excess from the corresponding racemic alcohol that contains a further chiral centre, which is not directly bound to the OH group, by oxidation in the presence of the catalyst according to any one of claims 1-11.

20. Process for the preparation of an enantiomerically enriched compound according to any one of claims 13-19, characterized in that isopropanol is used as the hydrogen donor.

21. Process for the preparation of an enantiomerically enriched compound according to any one of claims 13 - 16, characterized in that formic acid or a formic acid salt is used as the hydrogen donor.

22. Process for the preparation of an enantiomerically enriched compound according to claim 21, characterized in that the prochiral compound content is at least 0.2 mol per litre of the hydrogen donor.

# INTERNATIONAL SEARCH REPORT

Inter Application No
PCT/NL 00/00701

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01J31/22 C07B53/00 C07C323/58 C07C323/25 C07C317/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01J C07B C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 30 January 2001 | 09/02/2001 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Thion, M |

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